Excipients and additives: hidden hazards in drug products and in product substitution

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The excipients and additives in drug formulations have been described as inert because they do not have an active role in the prevention or treatment of particular ailments. This has led to the misconception among physicians, pharmacists, drug manufacturers and the public that excipients are harmless and unworthy of mention. In fact, pharmacists are allowed to substitute drug formulations, without regard to the excipients, as long as they ensure that the active ingredients in the substitute are the same as those in the formulation prescribed. The inappropriateness of the term inert is becoming increasingly apparent as evidence of adverse reactions — some fatal — to excipients mounts. The likelihood that some "active" constituents, particularly erythromycin, have been blamed for such reactions deserves to be investigated. The public deserves to be better protected. For example, the United States has legislation requiring complete labelling of all food, drugs and cosmetics that incorporate more than one ingredient, no matter how innocuous the constituents are believed to be. In Canada, drug manufacturers are not even required to share this information with physicians or pharmacists when they introduce a new drug or reformulate a product already being marketed, nor are pharmacists required to disclose the contents of formulations that they prepare in the absence of commercially available products.

On dit souvent que l'excipient d'une préparation pharmaceutique est inerte parce qu'il n'exerce aucune action préventive ou curatrice contre une maladie donnée. D'où, parmi les médecins, pharmaciens, industriels pharmaceutiques et dans le grand public, l'illusion que l'excipient est inoffensif et indigne de mention. Le pharmacien a même le droit de substituer une autre préparation à celle que le médecin a prescrite, pourvu que les ingrédients soi-disant actifs soient les mêmes, sans considération de l'excipient. Pourtant, vu la fréquence apparemment en hausse des réactions indésirables, voire mortelles, à des excipients, il faut mettre en doute la justesse de l'adjectif "inerte" qu'on leur applique. Il est probable que certaines de ces réactions ont été à tort imputées à des principes actifs, telle l'érythromycine: la chose demande à être étudiée de plus près. Car la protection du public est en cause. Alors qu'aux États-Unis, par exemple, la loi exige l'étiquetage complet des ingrédients de tout aliment, médicament ou produit de beauté qui en compte plus d'un, quelle qu'en soit l'innocuité présumée, ce n'est pas le cas pour les médicaments au Canada: le fabricant n'est pas tenu de passer ces renseignements au médecin ou au pharmacien lorsqu'il lance une nouvelle préparation ou qu'il modifie la formule d'une préparation qui existe déjà, et le pharmacien n'est pas tenu non plus de dévoiler le contenu des médicaments qu'il prépare *secundum artem*.

Most pharmaceutical products are a combination of constituents. In addition to the active or therapeutic ingredients, product formulations contain a number of "inert" materials known as additives or excipients. Classified according to the part they play in the finished product, the excipients include diluents, binders, lubricants, disintegrators, colours, flavours, sweetening agents etc.

"Dorland's Illustrated Medical Dictionary", 26th edition, defines an excipient as "any more or less inert substance added to a prescription in order to confer a suitable consistency or form to the drug; a vehicle"[1] and an additive as "a substance . . . preservative, or vitamin, added to another substance to improve its appearance, increase its nutritional value, etc.".[2] The inappropriateness of the term inert has become increasingly apparent: excipients may be active ingredients, though not in the pharmacologically accepted sense of components intended to affect the structure or function of the body in a way that contributes to the diagnosis, cure, mitigation or prevention of disease.[3]

In general the potential for adverse reactions to excipients has not been well recognized, probably because of both lack of knowledge about the excipients in products and, more importantly, the misconception that these substances are harmless and, therefore, unimportant. This misconception has contributed to the general acceptance that drug substitution is safe, practical and economical as long as the active ingredients remain constant.

"Epidemics" of adverse reactions due to toxic "inert" substances or

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changes in drug formulations were reported as early as the 1930s.[4,5] Although recent advances in biochemistry and in diagnostic procedures have expanded our understanding of the role that various constituents of drug preparations play in both the treatment of disease and the production of complications, adverse reactions to inert substances have not been eliminated.

Practising physicians encounter patients who prefer one product to another having identical active ingredients. Frequently the preference results from the patient's having had an adverse reaction to one of the products. This phenomenon was largely unrecognized until 1971, when Lockey[6] reported a case of severe headaches and protracted gastrointestinal disturbance associated with the ingestion of Premarin. At that time Premarin's formulation contained 28 ingredients, of which only one, the conjugated estrogen, was considered active. Included in the formulation was the yellow dye FD&C (Food, Drug, and Cosmetic [Act] — USA) no. 5, commonly known as tartrazine. Lockey confirmed that the patient was reacting solely to the tartrazine and could, by washing the colouring agent from each tablet, continue taking the medication without adverse effects. Had Lockey not tested the patient against all components of the formulation, the adverse effects would almost certainly have been attributed to the active ingredient. More importantly, the patient would have been denied useful treatment.

Tincture of orange

Similarly, one of us (D.G.H.S.), in a consulting pediatric practice, found tincture of orange to be hazardous. A patient was referred for advice and help in the management of recurrent upper respiratory tract infections. The infections tended to be refractory because the patient was hypersensitive to penicillin and its derivatives and had also demonstrated gastrointestinal intolerance to other antimicrobial medications. Pneumococcal infection was confirmed, and oral administration of 5 mL of liquid erythromycin — Erythrocin 125, each millilitre of which contains 25 mg of erythromycin — was prescribed. Immediately after ingesting the first dose of the suspension, the patient suffered severe abdominal pain, nausea and vomiting. Because of scepticism about an allergy to erythromycin, Erythrocin 250, each millilitre of which contains 50 mg of erythromycin, was substituted at the same dosage. This formulation produced none of the previous symptoms.

Several months later a local pharmacist disregarded the "No Substitution" order on the prescription for the patient and substituted the offending formulation. The patient's pain, nausea and vomiting recurred. Told of the consequences of the substitution, the pharmacist responded as have many practitioners in the past: "The active ingredient is the same; the colouring and flavouring don't matter."

During an outbreak of pertussis on an Indian reserve, Georgina Island, Ontario, the regional officer of health prescribed Erythrocin 125 as prophylaxis and had complaints of similar gastrointestinal symptoms from several of the children. Of the two children who required hospital admission for pertussis, one also experienced intolerance to the one formulation of erythromycin (Erythrocin 125) but not the other (Erythrocin 250) (D.G.H.S.: unpublished data, 1982).

A review of the records of the same consulting pediatric practice disclosed that during the previous 15 years 16 patients with confirmed hypersensitivity to penicillin had manifested the same type of intolerance to Erythrocin 125. Communication with the manufacturer, Abbott Laboratories, Limited, revealed that the sole difference between the two erythromycin formulations was the colouring and flavouring agent, tincture of orange. This alcohol extraction of orange peel, available commercially from several sources, was present in the offending formulation but not in the other, which is formulated with cherry syrup. There is no tartrazine in either preparation.

Tincture of orange is sometimes used by pharmacists to formulate suspensions for infants when a commercially prepared suspension is not available. For example, a 6-week-old boy with congenital heart disease and heart failure who had been receiving digoxin and Aldactazide (spironolactone – hydrochlorothiazide) in a suspension formulated by the hospital began vomiting after being given the medication provided by a local pharmacy. The local pharmacist had substituted tincture of orange for cherry syrup. Reversion to the cherry formulation resolved the problem immediately and completely (D.G.H.S.: unpublished data, 1981).

In short, gastrointestinal disturbance attributed to erythromycin and other medications formulated with tincture of orange should be reassessed.[7]

Metabisulfite

Two papers presented at the annual meeting of the American Society of Allergy[8,9] described adverse reactions to metabisulfite, an antioxidant widely used in the food and drug industry. The first paper described four patients with chronic asthma who suffered acute asthma attacks following the ingestion of certain foods and wines. When challenged with each ingredient separately, the patients reacted only to capsules of sodium metabisulfite. The second paper discussed two cases, one of which was similar to the first four. The second involved a patient who had respiratory arrest following intravenous administration of dexamethasone sodium phosphate (Decadron) combined with aminophylline (on four occasions) and, later, metoclopramide hydrochloride (Maxeran) (on one occasion). Double-blind challenge with 500-mg capsules of sodium metabisulfite, which is present in the dexamethasone and metoclopramide preparations but not in the aminophylline formulation, resulted in identical clinical episodes.

Polyethylene glycol

Another excipient to which adverse reactions have been reported is polyethylene glycol, an "inert" ingredient in drugs, shaving lotions, milk shakes etc. Kwee and Dolovich[10] reported their experience with a 36-year-old man who in 6 years had five documented episodes of anaphylaxis characterized by hypo-

tension, loss of consciousness and major generalized seizures. The patient reported a past history of hives following the topical use of shaving lotions and perfumes and remembered having taken a multivitamin tablet before the most recent episode. The patient was challenged with the individual constituents of the tablet, and polyethylene glycol was identified as the offending agent.

Benzyl alcohol

In 1982 the director of drugs and biologics of the US Food and Drug Administration notified hospital pharmacists of reported problems with benzyl alcohol,[11,12] a preservative found not only in multidose vials of sterile water and sodium chloride for parenteral use but also in many parenteral drug formulations, such as Solu-Cortef (hydrocortisone sodium succinate), morphine, heparin and Valium (diazepam). Deaths had occurred in premature infants weighing less than 1250 g; the infants died after the development of a condition named the gasping syndrome, which was eventually attributed to benzyl alcohol. Benzyl alcohol had also been implicated in exacerbation of asthma following the intravenous injection of Solu-Cortef.[13] When preparations containing benzyl alcohol were removed from nurseries for premature infants, reports of the gasping syndrome and related deaths stopped.

Questions subsequently arose concerning complications and complaints associated with the epidural administration of morphine for intractable pain. Studies to investigate whether these problems also stem from adverse reactions to benzyl alcohol are under way in Canada.

Propylene glycol

Propylene glycol, a polyalcohol, is widely used as a solvent in cosmetics, lotions, ointments and drugs, including many injectable formulations (e.g., of benzodiazepines, digoxin, dimenhydrinate, pentobarbital, phenobarbital and phenytoin), as well as co-trimoxazole preparations for oral use, erythromycin ethylsuccinate and a number of multivitamin products. This agent is generally considered to be a stable, pharmacologically inert substance with low systemic toxicity.[14] However, it was reported to be associated with systemic toxic effects in 1970[15] and, more recently, with a protracted seizure unresponsive to anticonvulsant medication.[16] In the latter case the patient's electroencephalogram, grossly abnormal during the seizure, reverted to normal when the exposure to propylene glycol was stopped.

Azo dyes

Although in the United States preparations including tartrazine must, by law, be labelled accordingly, no such requirement exists in Canada. In 1982, 450 Canadian pharmaceuticals contained tartrazine,[17] though the number was declining as the recognition of adverse reactions spread. However, other aniline or azo dyes, including amaranth, sunset-yellow, FD&C no. 6 and new coccine, have also been implicated in adverse reactions.[18] These dyes are present not only in pharmaceuticals but also in dairy products, juices, candies, food-colouring kits, cosmetics and toiletries.

When a generic rifampicin–isoniazid preparation caused a reaction and the patient showed no reaction to either rifampicin or isoniazid administered as separate preparations, the excipients were investigated. The combination product contained only a minute amount of sunset-yellow, 0.76 mg per tablet, but challenge with 1 mg of the dye resulted in identical gastrointestinal tract signs and symptoms, which began 6 hours after ingestion and persisted for 12 hours.[18] This azo compound is closely related chemically to tartrazine and has now been substituted for it in many formulations.

Discussion

The lack of understanding of the importance of excipients[19] is demonstrated with a relatively new antihistamine–decongestant. The 1984 edition of the "Compendium of Pharmaceuticals and Specialties"[20] lists the contents of both the liquid and tablet preparations as two — the antihistamine and pseudoephedrine. In fact, the syrup contains, in addition to the two active ingredients, 11 excipients, 6 of which have been implicated in adverse reactions. The tablet has four excipients, two of which are known to cause reactions (D.G.H.S.: unpublished data, 1983–84).

The hazards of excipients are not limited to new drug products and drug substitutions: they extend to undisclosed changes in drug formulations. Within the past 15 months two preparations — an aqueous aminophylline formulation and an anticonvulsant suspension — widely used in the practice of pediatrics were reformulated and caused adverse reactions that were reported to the Adverse Drug Reaction Program of the Ontario Medical Association. In neither case were the pertinent professions, medicine and pharmacy, notified. In fact, it was difficult to obtain specific information about the formulation changes.

Physically any drug product is the sum of its individual components. Pharmacologically, however, a drug does not include its excipients. The fundamental dictum of therapeutics is that any substance producing an effect has the potential for side effects; this dictum must be applied to the so-called inert excipients. The increasing numbers of adverse side effects should lead to purer drug formulations in the future.

Although Lockey[21] had reported "allergic" reactions to tartrazine in 1959, it was not until 1980 that labelling regulations in the United States required documentation of the presence of this dye; such regulations are not in effect in Canada. Yet the known adverse reactions to this agent and to the other excipients we have cited — a list that is certainly not all-inclusive — clearly indicate that the time has come for drug manufacturers to disclose to physicians and pharmacists all ingredients of all formulations, both new and revamped. The present information vacuum has contributed to unnecessary illness and even fatalities and is no longer acceptable.

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Addendum

After this article was published we noticed a misstatement in the abstract. In the sentence beginning "For example, the United States has legislation requiring complete labelling of all food, drugs and cosmetics that incorporate more than one ingredient" the word "some" should be substituted for the word "all". US regulations require that the presence of tartrazine and a few other excipients and additives be indicated on the label but do not require that all possible excipients and additives be given on the label.

The Health Protection Branch of the Department of National Health and Welfare reviewed its policy on tartrazine in Information Letter #634 (Sept. 10, 1982). It concluded that "colouring agents in drugs should not present a hazard to health and that their concentration should be kept to the minimum for purposes of product identification". It also stated that "manufacturers are (being) asked to make a declaration of the presence of tartrazine in their products to the C.Ph.A.", which would then be published in the "Compendium of Pharmaceuticals and Specialties".

For the manufacturer of a new drug or proprietary medicine to obtain an "identification number" Canadian drug regulations require that all submissions contain a quantitative list of ingredients, including colouring agents. Although such information is regarded as confidential, the Health Protection Branch has been instrumental in bringing the consumer–physician and the manufacturer together in difficult cases.